REMARKS

Claim Amendments

Applicants have amended claim 1 (and claims that depend therefrom) for clarity and to more distinctly claim the subject matter that applicants consider to be the elected invention. As amended, claim 1 recites limitations formerly in original claim 2 (currently amended) and claim 5 (currently canceled). In particular, amended claim 1 recites that the host cell expresses at least one glycosidase activity, and that the method results in the production of recombinant glycoproteins having attached N-glycans comprising $GlcNAcMan_xGlcNAc_2$ core structures, wherein X is 3, 4, or 5. In addition, claims 3 and 6 have been amended to correct claim dependencies; claims 2, 3, 7 and 12 have been amended to improve their form; claim 33 has been amended to remove unnecessary claim limitations; and claims 40 and 43 has been amended to correct inadvertent typographical errors. Support for these amendments can be found throughout the specification as originally filed and none adds new matter (see, *inter alia*, paragraphs 112-113, 141-143 and associated Figures). Claims 2 and 13 have been canceled, claims 47-58 and 60 have been withdrawn for being drawn to unelected subject matter (discussed in further detail below), and claims 61-65 have been newly added. Support for claims 61-63 may be found throughout the specification; e.g., paragraphs 164-168 (claim 61; GnT III); paragraphs 56, 68, 164 and Figure 30 (claim 62; immunoglobulins); paragraphs 207-211 (immunoglobulin glycoproteins with bisecting GlcNAc). Support for claims 64 and 65 may be found, e.g., at paragraphs 112-113 and 141-143.

Restriction Requirement

The Examiner alleges that the invention contains claims directed to twenty-two (22) different inventions. According to the Examiner, the inventions listed in the 22 different groups are patentably distinct because they do not recite a single general inventive concept under PCT Rule 13.1 as they lack the same or corresponding technical features. Thirteen (13) of the 22 groups are

said to be drawn to patentably distinct methods for producing a human-like glycoprotein in a non-human eukaryotic host cell:

- **Group I** (claims 1-17 and 46) drawn to a method for producing a human-like glycoprotein in a non-human eukaryotic host cell comprising diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure, and to a human-like glycoprotein made by said method; and

- **Group II** (claims 1, 18 and 19) drawn to a method as in **Group I** wherein the host cell is further deficient in expression of initiating alpha-1,6 mannosyltransferase activity;

- **Group III** (claims 1 and 20) drawn to a method as in **Group I** wherein the host cell further expresses GnT1 UDP-GlcNAc transporter activities;

- **Group IV** (claims 1 and 21) drawn to a method as in **Group I** wherein the host cell further expresses UDP- or GDP-specific diphosphatase activity;

- **Group V** (claims 1, 22 and 23) drawn to a method as in **Group I** further comprising the steps of isolating the glycoprotein and subjecting it to further glycosylation in vitro;

- **Group VI** (claims 1 and 24-36) drawn to a method as in **Group I** further comprising the step of introducing into the host cell a nucleic acid molecule encoding one or more enzymes involved in the production of GlcNAcMan3GlcNAc2 or GlcNAc2Man3GlcNAc2;

- **Group VII** (claims 1 and 37-40) drawn to a method as in **Group I** further comprising the step of introducing into the host cell a nucleic acid molecule

encoding one or more enzymes involved in the production of GlcNAcMan4GlcNAc2;

- **Group VIII** (claims 1 and 41-42) drawn to a method as in **Group I** further comprising the step of introducing into the host cell a nucleic acid molecule encoding one or more enzymes involved in the production of GlcNAc2Man3GlcNAc2;

- **Group IX** (claims 1 and 43) drawn to a method as in **Group I** further comprising the step of transforming the host cell with at least one nucleic acid molecule encoding at least one mammalian glycosylation enzyme;

- **Group X** (claims 1 and 44) drawn to a method as in **Group I** further comprising the step of introducing into the host cell a nucleic acid molecule encoding one or more enzymes involved in the production of GlcNAc2Man3GlcNAc2;

- **Group XI** (claim 45) drawn to a host cell produced by the method of claim 1 **(Groups I-X)** or claim 44 **(Group X)**;

- **Group XXI** (claim 59) drawn to a method for producing a human-like glycoprotein in a non-human eukaryotic host cell comprising the steps of diminishing or depleting the activity of an alg gene in the host and introducing into the host at least one glycosidase activity; and

- **Group XXII** (claim 60) drawn to a method for producing a human-like glycoprotein having an N-glycan comprising at least two GlcNAcs attached to a trimannose core.

According to the Examiner, the above claimed methods "are distinct from each other as each requires different and distinct method steps." (Office Action, pages 5-6). Applicants respectfully traverse. While certain of the dependent claims require different and distinct additional

steps, there is nonetheless a technical relationship among the inventions that involves at least one common or corresponding technical feature.

In particular, and at least with respect to method claims that have been listed in Groups I-X and XXII and product-by-process claims listed in Groups I and XI, there is a single common inventive concept under PCT Rule 13.1: each of those methods requires the technical step of "*diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure*" – a feature that is recited in claim 1 and required in each claim that depends from claim 1 (e.g., claims 2-44). Claim 59 (Group XXI) recites an embodiment of this common technical feature ("comprising the step of diminishing or depleting from the host cell an *alg* gene activity") because alg activity is an "*enzyme in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure.*" The application as originally filed discloses making host cell mutations in one or more of the *alg 3, alg 9* and *alg 12* genes to diminish or deplete "the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure" as required by the claims.

This common technical feature -- *diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure* -- also defines the contribution of the claimed invention over the cited prior art. The Examiner contends that Nakayama et al., *EMBO J.* 11:2511-2519 (1992) ("Nakayama") teach an *och1* mutant in *S. cerevisiae* that *och1* is deficient in alpha-1,6 mannosyltransferase activity which has the ability to make more mammalian like glycoproteins. Nakayama, however, is irrelevant to the claimed invention because the alpha-1,6 mannosyltransferase enzyme encoded by the *OCH1* gene does NOT transfer a sugar residue to a lipid-linked oligosaccharide structure, the common technical feature of the above discussed method claims (*see e.g.*, paragraphs 5-7 of published application US2005/0170452 and original claims 18 and 19.)

Accordingly, claims 1-44 all relate to a single invention having a common technical feature that defines the invention over the prior art and should be rejoined. Claims 45 and 46 should also be rejoined as they refer to host cells made using the claimed methods and glycoproteins produced by those methods. And claim 59 also shares that common technical feature and hence is drawn to the same inventive concept.

Applicants respectfully request, for the above reasons, that the Examiner rejoin claims of Groups I – XI, XXI and XXII as those claims share one common technical feature and should thus be examined together under the unity of invention standard of the PCT.

To expedite prosecution, Applicants hereby provisionally elect Group I claims (original claims 1-17 and 46; corresponding to claims 1, 4, 6-12, 14-17, 46 and 61-65 submitted herewith), with traverse. In view of the restriction requirement, Applicants hereby withdraw claims 47-57 and 60 from consideration in the instant application as non-elected subject matter without waiver of their right to continue to prosecute and to obtain claims to the non-elected subject matter either in this application or by filing divisional or continuing applications claiming priority and benefit from this application.

Election of Species Requirement

Further, in the Examiner's opinion, the application contains claims directed to a multitude of patentably distinct species of the claimed invention. In this regard, the Examiner points to claims 6, 21, 24, 25, 28, 30, 36, 39, 40, 43 for reciting different glycosylation enzymes; to claim 5 for reciting distinct N-glycans; to claim 7 for reciting distinct glycosidases and glycotransferases; to claims 8 and 9 for reciting distinct diminished or depleted enzymes; to claims 12-15 for reciting distinct sugar residues; to claim 17 for reciting distinct host cells; to claim 25 for reciting distinct mannosidases, and different alpha-1,2 mannosidases from distinct organisms; to claim 29 for reciting distinct glycosyltransferases; to claim 32 for reciting distinct signal targeting peptides; to claim 33 for reciting distinct catalytic domains; and to claims 37 and 38 for reciting distinct

mannosyltransferases. The Examiner requires applicants to elect a single species from each of the above claims.

In response to the election of species requirement, ***for search purposes only***, applicants provisionally elect the following species, with traverse:

- claims 6, 21, 24, 25, 28, 30, 36, 39, 40, 43 (different glycosylation enzymes):
  alpha-1,2 mannosidase (claims 6, 7, 25, 39)
  GnTI (claims 24, 28, 39, 43)
  UDP-diphosphatase (claims 21 and 36)
  UDP GlcNAc transporter (claim 39)
  alpha-1,3 mannosidase (claim 40)

- claim 5 (distinct N-glycans): There is only one glycan structure recited in claim 5, which is GlcNAc2Man3GlcNAc2.

- claim 7 (distinct glycosidases and glycosyltransferases): alpha-1,2 mannosidase

- claims 8 and 9 (distinct diminished or depleted enzymes): dolichyl-P-Man:$Man_5GlcNAc_2$-PP-dolichyl alpha-1,3 mannosyltransferase

- claims 12-15 (distinct sugar residues): GlcNAc

- claim 17 (distinct host cells): *Pichia pastoris*

- claim 25 (distinct mannosidases; different alpha-1,2 mannosidases from distinct organisms): mouse alpha-1,2 mannosidase

- claim 29 (distinct glycosyltransferases): GnT I

- claim 32 (distinct signal targeting peptides): mannosyltransferase

- claim 33 (distinct catalytic domains): GnT I

- claims 37, 38 and 39 (*lacking* distinct mannosyltransferases): α-1,6 mannosyltransferase

Applicants traverse-in-part the Examiner's characterization of certain claims being generic with respect to certain claim features. For example, the Examiner states that claim 6 is generic for N-glycans, but claim 6 specifies that the host cell produces a GlcNAc3Man3GlcNAc2 structure. Further, the Examiner states that claim 9 is generic for diminished or depleted enzymes, yet claim 9 specifies that the host cell is diminished or depleted in dolichyl-P-Man:$Man_5GlcNAc_2$-PP-dolichyl alpha-1,3 mannosyltransferase activity.

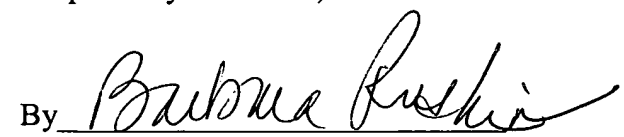
Further, applicants note that claims 3-27 and 30 read on the elected species of a CMP-Sia biosynthetic enzyme, but only claims 7-8 and 17 refer to species of enzymes involved in the CMP-biosynthetic pathway; claims 11, 25-27 and 31 read on the elected species of the therapeutic protein, but only claims 11 and 25 refer to species of therapeutic proteins; claims 1-31 read on the elected species of the host cell, but only claims 9 and 18 refer to species of host cells.

Applicants have filed concurrently herewith a petition for a four-month extension of time. Please charge our Deposit Account No. 06-1075, under Order No. 001634-0005, from which the undersigned is authorized to draw, for the requisite fee of $1590.00 under 37 C.F.R. § 1.17(a)(4)

and to charge payment of any additional fees required in connection with the papers transmitted herewith, or to credit any overpayment of same to the above Account.

Dated: November 29, 2006

Respectfully submitted,

By 

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